34. (previously added) The liposome delivery system of Claim 1, comprising PEG_{2000}-distearoylPE, cholesterol, distearolylPC and bis-$SorbPC_{17,17}$.

35. (previously added) The liposome delivery system of Claim 1, comprising PEG_{2000}-distearoylPE, distearolylPC and bis-$SorbPC_{17,17}$.

36. (new) A liposomal delivery system of Claim 1 wherein only about 5% of lipids are polymerized to cause destabilization of the liposomal membrane.

REMARKS

Entry of this amendment is respectfully requested. No new matter is added by the amendment, because the amended application is fully supported by the application as filed. More specifically, the amended Claims 1 and 27 are supported by the disclosures at least on pages 19, 20 and 21 and the new Claim 36 is supported by the disclosure at least on page 17.

The rejection under 35 USC 102(b)

Claims 1, 4, 9-11, 16-17, 19 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamparski (Biochemistry, vol. 31., 1992). The Examiner alleges that Lamparski discloses liposomes containing a phospholipid and a polymerizable colipid and that the polymerizable lipid upon polymerization with UV radiation polymerizes and destabilizes the liposomes thereby leaking the contents.

Claim 1 has been amended to recite the requirement that lipid and colipid form preexisting lipid domains wherein the colipids are clustered in discrete domains. In addition, Claim 1 calls for the use of ionizing radiation.

The subject matter of the amended Claim 1 and Lamparski are different in many aspects.

First, the use of an ionizing radiation is not disclosed in Lamparski. In fact, the Examiner himself even commented that Lamparski teaches only the application of UV radiation and not ionizing radiation, such as X-rays (see pages 5 and 7 of the final office action).

Secondly, Lamparski does not disclose or in any way suggest that the lipid and colipid may form preexisting lipid domains wherein the colipids are clustered in discrete domains. The Examiner states that the distribution of the lipids (whether random or discrete domain) is temperature dependent, therefore the distribution of lipids in the prior art preparations would be as "discrete domains" below the room temperature. The Applicants respectfully point out that the global transition temperature of the liposomes disclosed in Lamparski are substantially below the room temperature and the experimental temperature is 25°C. Since the experiments were *not* carried out at substantially below the room temperature, Lamparski does *not* expressly or inherently disclose *preexisting* discrete domains in the liposomes.

Applicants also wish to point out that Lamparski teaches the photoinduced phase separation between the lipids and colipids which *creates* domains of lipids and colipids as mentioned above. (See p. 691, column 2, under Discussion, second paragraph). Therefore, the Lamparski reference does not disclose the preexistence of lipid and colipid domains prior to polymerization.

Furthermore, the term "discrete domains" of polymerizable colipids is defined on page 17 of the specification to mean "for the purpose of the specification and claims, polymerizable colipids *clustered* together into groups[.]" The specification clearly states that the colipids are *clustered* in discrete domains. In addition, the plain meaning of the

term "cluster" means "a group of the same of similar elements occurring closely together " or "bunch". Webster's New College Dictionary 213 (2001). The specification provides additional example of domain formation on page 6 which states, "The polymerization of two (or multi) component lipid bilayers, with one polymerizable and other nonpolymerizable component(s), can cause lipid domain formation. The polymerizable lipids form covalently linked domains as the reaction proceeds, which in turn produces domains of the nonpolymerizable component(s)."

In this respect, MPEP §2111.02 states, "Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage. *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947)." In addition, "When not defined by applicant in the specification, the words of a claim must be given their plain meaning. In other words, they must be read as they would be interpreted by those of ordinary skill in the art. *In re Sneed*, 710 F.2d 1544, 218 USPQ 385 (Fed. Clr. 1983)."

MPEP §2131 further provides, "'A claim is anticipated only if *each* and *every* element as set forth in the claim is found, either expressly or inherently described in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as contained in the ... claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim[.]"

MPEP §2112 additionally provides, "The fact that a certain result of characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that

result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)." In addition, it provides, "The inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

In this case, there is no disclosure, either inherent or explicit, in Lamparski which would indicate the formation of preexisting lipid domains in which *the colipids are clustered in discrete domains.* Therefore, Applicants disagree with the Examiner's suggestion that each and every element as set forth in the claims is disclosed in Lamparski, either expressly or inherently, because already at least two key elements (i.e., requiring the lipid and the polymerizable colipid to preexist in the form of discrete domains within the liposome and the exposure to ionizing radiation), are *not* disclosed in Lamparski.

The amendment to Claim 1, therefore, is believed to overcome the rejection under 35 USC 102(b) and the Examiner is respectfully requested to reconsider and withdraw the rejection.

The rejection under 35 USC 103(a)

Claims 1, 4-5, 9-11, and 16-31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lamparski. The Examiner alleges it would be obvious to one of ordinary skill in art to use the liposomes of Lamparski for the delivery of the diagnostic or therapeutic agents with a reasonable expectation of success. Furthermore, the Examiner states that *in the absence of showing the criticality*, it is *deemed obvious* to

one of ordinary skill in art to use any form of ionization as long as they polymerize the lipid. Responding to this rejection, Applicants wish to point out that neither Lamparski, nor any other evidence of record, establishes a *prima facie* case of obviousness. More specifically, the amended Claim 1 now requires that the formation of preexisting lipid domains wherein the colipids are clustered in discrete domains. In addition, Claim 1 calls for the use of ionizing radiation. None of these features is disclosed or in any way suggested in Lamparski. In this regard, "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." (see MPEP §2142).

Claims 5-8 and 12-15, 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski in view of Woodle (BB 1992). This rejection is also respectfully traversed. In view of the fact that Claim 1 requires formation of the preexisting lipid domains and exposure to ionizing radiation, there was no suggestion in Lamparski or Woodle to make the suggested combination or modification. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." (see MPEP §2143.01)

Claims 1 and 4-35 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lamparski by itself or in combination with Woodle in view of Hallahan (US patent no. 6,159,443). Applicants respectfully disagree. The Examiner alleges that Hallahan is combined to show the use of X-rays as ionizing radiation for the release of active agent from liposomes to the selective tissue. However, the combination of the references in the manner suggested by the Examiner would change the principle of operation disclosed in Hallahan. Hallahan does not teach the use of X-rays as ionizing radiation

for the release of active agent from liposomes to the selective tissue as the Examiner alleges. In fact, Hallahan teaches the use of ionizing radiation targeted at tumor sites to induce platelet aggregation as a way to control cellular adhesion molecules involved in tumor growth. (column 6, lines 18-27). Hallahan does not suggest the use of X-rays to polymerize any type of lipid. Instead, Hallahan teaches a method of delivering an active agent, such as chemotherapeutic or radiosensitizing agent, using a delivery vehicle that can be administered *before*, after or during the exposure to the ionizing radiation to the targeted tissues or cells. Thus, the exposure of the targeted tissues to the ionizing radiation does not depend on whether the active agent has already been administered, and in particular, whether a liposome is used as a delivery vehicle for the active agent. Accordingly, the Examiner's suggested combination would change the principle of operation of Hallahan, because Hallahan does not teach the use of X-rays to polymerize the lipid.

Hallahan does not, in fact, teach one of ordinary skill in the art what the examiner opines it teaches. Hallahan would not have prompted one of ordinary skill in the art to combine the teachings of its use of ionizing radiation to induce platelet aggregation with that of Lamparski and Woodle to use the ionizing radiation to polymerize lipids to release active agent from liposomes.

Consequently, there exists no intrinsic basis or extrinsic justification for the proposed combination of Hallahan with Lamparski and Woodle and *prima facie* obviousness has not been established. Applicants respectfully traverse the rejection of those claims.

Conclusion

Since the amended Claim 1 is believed to be allowable, claims directly or indirectly dependent from the amended Claim 1 (i.e., Claims 4-36) are also allowable,

Entry of the amendment, and reexamination, reconsideration, and early allowance of claims 1 and 4-36 are therefore respectfully requested. Applicants note that the amendments herein do not indicate Applicants' agreement to the propriety of the rejections, and Applicants reserve the right to pursue claims such as those presented previously in a related application.

Please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641.

Respectfully submitted,

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